PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Clinical Efficacy of Transcutaneous Electrical Nerve Stimulation (TENS) for Acute and Chronic Pain: A Protocol for a Meta-Analysis of Randomized Controlled Trials (RCTs)
AUTHORS	Johnson, Mark; Jones, Gareth; Paley, Carole; Wittkopf, Priscilla

VERSION 1 – REVIEW

REVIEWER	Andrew Beswick University of Bristol, UK
REVIEW RETURNED	15-Apr-2019

GENERAL COMMENTS	The authors of the protocol have extensive experience in the study of TENS for pain conditions. Drawing together research from different acute and chronic pain conditions seems reasonable as TENS works through stimulation of peripheral nerves and not mechanisms unique to specific conditions. The authors have a clear understanding of what constitutes TENS and what interventions are relevant to the review. It is good to see that pain outcome measures will be dichotomised to identify those with successful treatment rather than relying on group mean differences. In other reviews of pain management, cancer-pain is excluded. Is it appropriate to include it here? (I don't know) The authors propose a meta-analysis of RCTs that they identify from previous systematic reviews. This is a reasonable approach. However, like RCTs, systematic reviews vary in quality and should be assessed using a risk of bias tool such as AMSTAR2 or ROBIS. If there is no review of good quality, a new search and systematic review will be required. Similarly, previous systematic reviews may be out of date. More recent TENS RCTs should be identified to supplement those found in older reviews. In fact, this would be a strength of the proposed review as there may be good quality recent RCTs. It would be a shame to miss them. The methods, abstract and search strategy would need to be altered to accommodate this. Please state that it will be registered in PROSPERO Methods Page 7 Line33 "However, we will give credence to RCTs that deliver at least two weeks of treatment and have a duration of at least eight weeks." I was not sure what this means – will these studies be treated as best practice in a subgroup analysis or will interventions with less intervention be excluded.

	Also Page 9 Line 20 “We will give credence to RCTs that attempt to assess the credibility of placebo TENS.” Again, it is not clear what “credence” means here. Evaluation of TENS Treatment Effects] Page 8 Line 52 Will you include studies where 2 TENS regimens have been compared, possibly both against untreated? Or where TENS is “usual care” against a new pain management strategy? Any thoughts on network meta-analysis? I don’t know the literature but in some systematic reviews this allows combination of direct and indirect comparisons. Network meta-analysis may not be appropriate here but may be worth acknowledging. Types of outcome measures Page 9 Line 25 As the review includes a wide range of pain-related conditions, there may be condition-specific outcomes reported, e.g. WOMAC pain in osteoarthritis and others in back pain, cancer etc. These may be a good pain outcome for the review as they are highly specific to the source of pain. Adverse effects – should be considered in relation to stopping of treatment? As well as serious adverse events. Please add in something about Author contact. Especially in more recent RCTs, authors should be able to clarify issues relating to inclusion, risk of bias and missing data. Emails will be sufficient. Page 5, line 40 – whether Page 5 Line 50. “Systematic reviews and meta-analyses are hindered by methodological weaknesses” – this is true, but in the context of this sentence I think this should say “Systematic reviews and meta-analyses are hindered by methodological weaknesses of included RCTs.” Page 5 Lines 39-40. “According to the Cochrane collaboration, trial arms with fewer than 200 participants in RCTs or fewer than 500 participants in meta-analyses are at a high risk of bias seriously undermining confidence in findings.” This isn’t from the Cochrane Handbook – it may come from PAPAS. They are not keen on studies with less than 50 patients which they exclude in sensitivity analyses at least. Cochrane Injuries Group advise “The information size is the number of participants required in a meta-analysis to reliably detect an intervention effect. This may be approximated by the sample size that would be needed for a single randomised controlled trial to detect the hypothesised intervention effect.” Including cross-over designs in systematic reviews in meta-analysis can be difficult. I wish the authors well with their proposed research which should provide good evidence on the value of TENS in the treatment of acute and chronic pain.

REVIEWER	Dr Gustavo C Machado Institute for Musculoskeletal Health, Sydney, Australia
REVIEW RETURNED	09-May-2019

GENERAL COMMENTS	Abstract 1. State which databases will be used for the searches. 2. Its seems strange to look for systematic reviews when you are able to research for original trials. It is likely that authors will reproduce any errors/selection bias of identified systematic reviews. Strengths and Limitations 1. The broad inclusion criteria of this systematic review means that different populations/conditions are likely to be included, so meta-analysis might not be possible/appropriate. 2. Another limitation is searching for previous systematic review rather than original trials. Introduction 1. Burden of chronic pain is described. What about the burden of acute pain? 2. Pooling of studies investigating many different conditions would lead to high heterogeneity and thus the results would not meaningful to be applied in clinical practice. I think this is a poor rationale for conducting this review. Perhaps the authors could twist this a little bit. The strength of this review is actually in providing end-users of research (eg clinicians, policy makers, and patients) with a unique source of information on the effects of TENS for any type of pain. Methods 1. The first primary outcome needs clarification. Should it be: proportion of patients reporting pain relief of 30% or greater...? Also, I was wondering where the decision of using 30% as a cut-off came from... Why not 20% or 15%? What if this data is not reported in the included trials? Would the authors ask for the raw data? 2. Second primary outcome seems more straightforward. 3. The thresholds used from IMMPACT seem to be for within-group difference, so it would not be appropriate to be used as a threshold for between-group difference, which is what the authors will get from he meta-analysis. Please clarify. 4. Why are the authors not planning to search for original trials instead of searching for systematic reviews? What if the previous systematic reviews had limitations in their search strategies (eg language and date restrictions) which are likely to introduce selection bias? I would recommend searching original randomised trials based on the inclusion criteria outlined in the methods. 5. In data synthesis. I would suggest planing to conduct random effects meta-analysis only considering the diversity of conditions/interventions to be included in this review. 6. Are the authors planning to conduct meta-regression to identify factors that influence heterogeneity likely to be found in the pooled analysis? Which factors are anticipated to influence the pooled effect size?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Andrew Beswick
Institution and Country: University of Bristol, UK Please state any competing interests or state 'None declared': None declared

The authors of the protocol have extensive experience in the study of TENS for pain conditions. Drawing together research from different acute and chronic pain conditions seems reasonable as TENS works through stimulation of peripheral nerves and not mechanisms unique to specific conditions. The authors have a clear understanding of what constitutes TENS and what interventions are relevant to the review. It is good to see that pain outcome measures will be dichotomised to identify those with successful treatment rather than relying on group mean differences.

In other reviews of pain management, cancer-pain is excluded. Is it appropriate to include it here? (I don't know)
Authors' Response: This is a very interesting point and we appreciate that there may be substantial differences in the context in which different types of pain are experienced (e.g. acute versus chronic, negligible versus life-threatening etc.) and that this has potential for high clinical and statistical heterogeneity. It is for this reason that we will conduct sub-group analyses where possible. We are approaching this review from the standpoint of pooling data irrespective of cause of pain in the first instance because pain is a complex phenomenon driven by socio-psycho-biological factors and evidence suggests that the linkage between pain experience and pathology is variable, even for acute pain. Many pains are secondary to medical conditions and classified accordingly into traditional pathological-based categories, e.g. chronic pain secondary to cancer, and although there are many similarities (and differences) in the final experience of pain, these can vary considerably for individuals with similar medical conditions. Thus, our approach is to evaluate pain outcomes from a phenomenological perspective supported by sub-group analyses.
Action: We have added further explanation of our approach to the section Introduction

The authors propose a meta-analysis of RCTs that they identify from previous systematic reviews. This is a reasonable approach. However, like RCTs, systematic reviews vary in quality and should be assessed using a risk of bias tool such as AMSTAR2 or ROBIS. If there is no review of good quality, a new search and systematic review will be required.
Authors' Response: We have re-focused our search for RCTs in line with comments from both reviewers and will now conduct a search for RCTs in parallel with a search for systematic reviews. This approach enables us to conduct a descriptive analysis of the inclusion or otherwise of RCTs between different systematic reviews, including our own.
Action: We have amended the Methods section to reflect this change in search strategy. We have added a sentence to the beginning of the Methods section to emphasise how we intend to use SRs in our review. We have strengthened the rationale for the need to undertake an 'all-encompassing' review and have emphasised the novelty of this approach, including limitations of previous systematic reviews in the Introduction section.

Similarly, previous systematic reviews may be out of date. More recent TENS RCTs should be identified to supplement those found in older reviews. In fact, this would be a strength of the proposed review as there may be good quality recent RCTs. It would be a shame to miss them. The methods, abstract and search strategy would need to be altered to accommodate this.

Authors' Response: We agree and accept the possibility of missing RCTs published since recent SRs on particular conditions. Hence, we have re-focused our search strategy to identify RCTs published from inception to present date, to be conducted in parallel with a search for systematic reviews.

Action: This has been articulated in the Methods section and the new search strategy added to the supplemental material

Please state that it will be registered in PROSPERO
Authors' Response: It has been registered in PROSPERO
Action: Registration number added to Abstract

Methods Page 7 Line33
"However, we will give credence to RCTs that deliver at least two weeks of treatment and have a duration of at least eight weeks." I was not sure what this means – will these studies be treated as best practice in a subgroup analysis or will interventions with less intervention be excluded.
Authors' Response: Thank you - we appreciate that this is vague.
Action: We have clarified in the section 'Types of studies'

Also Page 9 Line 20
"We will give credence to RCTs that attempt to assess the credibility of placebo TENS."
Again, it is not clear what "credence" means here.
Authors' Response: Thank you - we appreciate that this is vague.
Action: We have clarified in the section 'Criteria and Credibility of Placebo TENS'

Evaluation of TENS Treatment Effects] Page 8 Line 52
Will you include studies where 2 TENS regimens have been compared, possibly both against untreated?
Authors' Response: Yes, and we have a strategy for managing potential unit of analysis errors associated with double counting common comparison groups.
Action: This information has been added to the section 'Evaluation of TENS Treatment Effects'

Any thoughts on network meta-analysis? I don't know the literature but in some systematic reviews this allows combination of direct and indirect comparisons. Network meta-analysis may not be appropriate here but may be worth acknowledging.
Authors' Response: Indeed. It is likely that TENS will be compared with multiple treatments, so it is possible that we would be able to use the indirect and direct comparisons. Nevertheless, we cannot anticipate if we will be able to meet all assumptions needed to produce a network meta-analysis.
Action: We have acknowledged the possibility and intention of conducting a network analysis contingent on meeting transitivity assumptions ('Subgroup analysis' section).

Types of outcome measures Page 9 Line 25 As the review includes a wide range of pain-related conditions, there may be condition-specific outcomes reported, e.g. WOMAC pain in osteoarthritis and others in back pain, cancer etc. These may be a good pain outcome for the review as they are highly specific to the source of pain.
Authors' Response: We agree, and realise that we did not make this explicit in the bullet point 'Any participant-reported pain-related outcomes other than pain intensity' in the section 'Secondary outcomes'
Action: We have added this to the section 'Secondary outcomes'

Adverse effects – should be considered in relation to stopping of treatment? As well as serious adverse events.
Authors' Response: Yes
Action: We have added statement to the section 'Types of outcome measures'

Please add in something about Author contact. Especially in more recent RCTs, authors should be able to clarify issues relating to inclusion, risk of bias and missing data. Emails will be sufficient.

Authors' Response: Yes, of course
Action: Added to the section 'Data extraction and management'

Page 5, line 40 – whether
Authors' Response: Oops – thank you
Action: Corrected

Page 5 Line 50. "Systematic reviews and meta-analyses are hindered by methodological weaknesses" – this is true, but in the context of this sentence I think this should say "Systematic reviews and meta-analyses are hindered by methodological weaknesses of included RCTs."
Authors' Response: Thank you
Action: Corrected

Page 5 Lines 39-40. "According to the Cochrane collaboration, trial arms with fewer than 200 participants in RCTs or fewer than 500 participants in meta-analyses are at a high risk of bias seriously undermining confidence in findings." This isn't from the Cochrane Handbook – it may come from PAPAS. They are not keen on studies with less than 50 patients which they exclude in sensitivity analyses at least.
Cochrane Injuries Group advise. "The information size is the number of participants required in a meta-analysis to reliably detect an intervention effect. This may be approximated by the sample size that would be needed for a single randomised controlled trial to detect the hypothesised intervention effect."
Authors' Response: Thank you. We agree and are aware of the debate. We would like to follow the advice from PaPaS (summarised in an unpublished document from Andrew Moore titled 'Words on Small sample Sizes') to enable direct comparisons with previously published Cochrane reviews on TENS.
Action: We have amended our statement and have referenced the work of Moore et al. on which PaPaS advice is based.

Including cross-over designs in systematic reviews in meta-analysis can be difficult.
Authors' Response: We are aware of this. We do not expect TENS to 'cure' pain, but we do appreciate the possibility of carry-over effects. Nevertheless, we will follow procedures that we have used in previous Cochrane reviews. We have stated that we will include cross-over designs but intend only to enter the first period data into the meta-analysis.
Action: None

I wish the authors well with their proposed research which should provide good evidence on the value of TENS in the treatment of acute and chronic pain.

Authors' Response: Thank you for taking the time to produce some extremely helpful comments

Reviewer: 2
Reviewer Name: Dr Gustavo C Machado
Institution and Country: Institute for Musculoskeletal Health, Sydney, Australia Please state any competing interests or state 'None declared': I declare no conflicts of interest of any kind.

Please leave your comments for the authors below
Abstract
1. State which databases will be used for the searches.
Authors' Response: Thank you
Action: Databases added to Abstract

2. Its seems strange to look for systematic reviews when you are able to research for original trials. It is likely that authors will reproduce any errors/selection bias of identified systematic reviews.
Authors' Response: Our team debated this at length during conception of the study. We accept the comments from both reviewers that our original search strategy has the potential to miss RCTs. Hence, we have re-focused our search to capture RCTs published from inception to present day, and this will be conducted in parallel with a search for SRs.

For the record, our reasons for harvesting RCTs from previous SRs and screening these RCTs against our own eligibility criteria (and re-assessing using Cochrane's RoB tool) were to enable us to conduct a descriptive analysis of the inclusion or otherwise of RCTs between different systematic reviews, including our own. This mapping of eligibility between previously published reviews will provide insights to the extent of inconsistencies of RCTs in reviews on identical/similar conditions. We believed that we were unlikely to miss RCTs because many previous SRs (including Cochrane reviews) were recent and had undertaken broad literature searches that would capture all TENS studies. We would screen tables of excluded RCTs in all SRs against our eligibility criteria to mitigate against selection bias within SRs. However, we appreciate that this approach has limitations.

Action: The search methods and eligibility criteria have been amended in the Methods section and the search strategy for RCTs has been added to supplemental material. We have added sentences to relevant locations in the Methods sections to reflect the points made above and to emphasise how we intend to use SRs in our review. We have added clarity to the sections 'Types of studies' and 'Search methods for identification of studies' to highlight the reason for harvesting RCTs from previously published SRs. We have strengthened the rationale for the need to undertake an 'all-encompassing' review and have emphasised the novelty of this approach, including limitations of previous systematic reviews in the Introduction.

Strengths and Limitations
1. The broad inclusion criteria of this systematic review means that different populations/conditions are likely to be included, so meta-analysis might not be possible/appropriate.
Authors' Response: We recognize the potential criticisms associated our approach to pool data irrespective of population/condition and have referred to the tension between statistical power and clinical heterogeneity in the Introduction.
We appreciate that there may be substantial differences in the context in which different types of pain are experienced (e.g. acute versus chronic, negligible versus life-threatening etc.) and that this has potential for high clinical and statistical heterogeneity. It is for this reason that we will conduct sub-group analyses where possible. We are approaching this review from the standpoint of pooling data irrespective of cause of pain in the first instance because pain is a complex phenomenon driven by socio-psycho-biological factors and evidence suggests that the linkage between pain experience and pathology is variable, even for acute pain. Many pains are secondary to medical conditions and classified accordingly into traditional pathological-based categories, e.g. chronic pain secondary to cancer, and although there are many similarities (and differences) in the final experience of pain, these can vary considerably for individuals with similar medical conditions. Thus, our approach is to evaluate pain outcomes from a phenomenological perspective supported by sub-group analyses.
Action: We have strengthened the rationale and justification for our approach in the Introduction by amending the rationale to undertake an 'all-encompassing' review and emphasising the novelty of our approach, including limitations of previous systematic reviews.

2. Another limitation is searching for previous systematic review rather than original trials.
Authors' Response: We agree that this may be a limitation and have refocused our search to identify RCTs directly from electronic databases.

Action: We have emended the Methods section and added the new search strategy to the supplemental material.

Introduction
1. Burden of chronic pain is described. What about the burden of acute pain?
Authors' Response: Thank you for pointing our oversight
Action: We have added a sentence referring to the burden of acute pain to the Introduction.

2. Pooling of studies investigating many different conditions would lead to high heterogeneity and thus the results would not meaningful to be applied in clinical practice. I think this is a poor rationale for conducting this review. Perhaps the authors could twist this a little bit. The strength of this review is actually in providing end-users of research (eg clinicians, policy makers, and patients) with a unique source of information on the effects of TENS for any type of pain.
Authors' Response: Thank you for this comment and the offer of an additional twist on our rationale. The issue of high heterogeneity is something that our team debated at length at study conception. We appreciate that there may be substantial differences in the context in which different types of pain are experienced (e.g. acute versus chronic, negligible versus life-threatening etc.) and that this has potential for high clinical and statistical heterogeneity. It is for this reason that we will conduct sub-group analyses where possible. We are approaching this review from the standpoint of pooling data irrespective of cause of pain in the first instance because evidence suggests that the linkage between pain experience and pathology is variable, even for acute pain. Many pains are secondary to medical conditions and classified accordingly into traditional pathological-based categories, e.g. chronic pain secondary to cancer, and although there are many similarities (and differences) in pain processes, the final experience of pain can vary considerably for individuals with similar medical conditions. Thus, our approach is to evaluate pain outcomes from a phenomenological perspective supported by sub-group analyses.
Action: We have amended the section Introduction to further reflect these arguments

Methods
1. The first primary outcome needs clarification. Should it be: proportion of patients reporting pain relief of 30% or greater...?
Authors' Response: Thank you
Action: Primary and secondary outcomes have been amended accordingly

Also, I was wondering where the decision of using 30% as a cut-off came from... Why not 20% or 15%?
Authors' Response: This in line with recommendation of IMMPACT
Action: We have amended text and adjusted the order of paragraphs in the section 'Types of outcome measures' and 'Measures of treatment effect' to improve the clarity of communication.

What if this data is not reported in the included trials? Would the authors ask for the raw data?
Authors' Response: We will approach authors via e-mail
Action: Added to the section 'Data extraction and management'

2. Second primary outcome seems more straightforward.
Authors' Response: Indeed, the analysis of the continuous data is more straightforward.
Action: Nevertheless, we have amended the section describing data analysis of primary and secondary outcomes to improve consistency and clarity of our analysis.

3. The thresholds used from IMMPACT seem to be for within-group difference, so it would not be appropriate to be used as a threshold for between-group difference, which is what the authors will get from the meta-analysis. Please clarify.

Authors' Response: We will be conducting a responder analysis, in which we extract frequency data for participants reporting > 30% relief of pain for each intervention group to calculate risk ratio and risk differences. Ultimately a NNTB will be calculated. We have not set the threshold for the difference in proportion achieving 30% between groups. For continuous data we will calculate the difference between groups in the percentage change in pain intensity during treatment relative to baseline. This will enable us to classify according to IMMPACT criteria for clinically important change, as previously used in Cochrane reviews, where no important change < 15%, minimally important change 15% > 30%, moderately important change 30% > 50% and substantially important change ≥ 50%. This will be a classification of clinically important change rather than a threshold for significance level.
Action: We have amended the section 'Measures of treatment effect' section to improve clarity of our description of primary outcomes and how they will be analysed and classified according to IMMPACT.

4. Why are the authors not planning to search for original trials instead of searching for systematic reviews? What if the previous systematic reviews had limitations in their search strategies (eg language and date restrictions) which are likely to introduce selection bias? I would recommend searching original randomised trials based on the inclusion criteria outlined in the methods.
Authors' ResponseWe accept that our original approach to harvesting RCTs had potential to miss RCTs and have refocussed our search strategy accordingly as described in earlier responses to reviewers' comments
Action: The search methods and eligibility criteria have been amended in the Methods section and the search strategy for RCTs has been added to supplemental material. We have added sentences to relevant locations in the Methods sections to emphasise how we intend to use SRs in our review. We have added clarity to the sections 'Types of studies' and 'Search methods for identification of studies' to highlight the reason for harvesting RCTs from previously published SRs. We have strengthened the rationale for the need to undertake an 'all-encompassing' review and have emphasised the novelty of this approach, including limitations of previous systematic reviews in the Introduction.

5. In data synthesis. I would suggest planning to conduct random effects meta-analysis only considering the diversity of conditions/interventions to be included in this review.
Authors' Response: Thank you for your advice and we agree.
Action: We have made the amendments on 'Sensitivity analysis' and 'Assessment of heterogeneity' sections.

6. Are the authors planning to conduct meta-regression to identify factors that influence heterogeneity likely to be found in the pooled analysis?
Authors' Response: We will be conducting meta-regression contingent on data availability.
Action: We have added the intention to conduct a meta-regression and the factors that should be investigated to the 'Assessment of heterogeneity' section.

Which factors are anticipated to influence the pooled effect size?
Authors' Response: We anticipate that factors that may influence pooled effect size are clinical condition, acute vs chronic pain, optimal vs suboptimal TENS protocol and these factors will be analysed in a meta-regression.
Action: We have added the intention to conduct a meta-regression and the factors that should be investigated to the section 'Assessment of heterogeneity'.

Authors' Response: Thank you for taking the time to review our manuscript and to provide some extremely helpful comments

VERSION 2 – REVIEW

REVIEWER	Andrew Beswick University of Bristol, UK
REVIEW RETURNED	22-Aug-2019

GENERAL COMMENTS	The protocol reads well. Good luck with your research